Attorney's Docket No. 038151/203996

PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.:	10/088,538	Confirmation No.: 6926
Applicant(s):	Thomas N. Masters	
Filed:	June 10, 2002	
Art Unit:	1617	
Examiner:	Gregory W. Mitchell	
Title:	SOLUTION FOR THE PRESERVATION OF HEARTS	

Customer No.: 00826

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APPEAL BRIEF TRANSMITTAL
(PATENT APPLICATION – 37 C.F.R. § 41.37)

1. Transmitted herewith is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on November 11, 2005.

2. ☒ Applicant claims small entity status.

3. Pursuant to 37 C.F.R. § 41.20(b)(2), the fee for filing the Appeal Brief is:
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Janet F. Sherrill

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APPEAL BRIEF UNDER 37 CFR § 41.37

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed November 11, 2005.

1. ***Real Party in Interest.***

The real party in interest in this appeal is Charlotte-Mecklenburg Hospital Authority d/b/a Carolinas Medical Center, the assignee of the above-referenced patent application.

2. ***Related Appeals and Interferences.***

There are no related appeals and/or interferences involving this application or its subject matter.

3. ***Status of Claims.***

Claims 1-5, and 8 have been cancelled. Claims 6 and 9-14 are being appealed.

4. ***Status of Amendments.***

The claims have not been amended subsequent to the Final Rejection dated September 9, 2005. A pre-appeal brief request for review was filed on November 11, 2005 and denied on December 23, 2005.

5. ***Summary of Claimed Subject Matter.***

The Applicant has developed a new medicament and a method of using the medicament for preserving and storing a heart awaiting transplantation. *See, Specification at page 4, lines 4-16.* Independent Claim 6 claims a method for blocking apoptosis during preserving and storing a heart awaiting transplantation and requires perfusing the heart with a solution consisting essentially of a balanced isotonic solution, cyclosporin A in an amount from about 2.5 μm to about 10 μm per liter of solution; and water. Claims 7 and 9-10 are dependent upon Claim 6 and define preferred embodiments of the method. Independent Claim 11 and Claims 12-13 dependent thereon are directed to the medicament used in the method.

That the claimed medicament performs its intended function, that of preserving a heart awaiting transplantation for up to 24 hours, is abundantly clear from the experiments disclosed in the specification at pages 10-14, and shown in the results set forth in FIGS. 2-7. These *unexpected* results show that ATP and CP concentrations were remarkably reduced during preservation with cyclosporin A after 18 hours and 24 hours of preservation; as compared to preserving without cyclosporine A. *Note especially Figure 2.*

6. ***Grounds of Rejection to be Reviewed on Appeal.***

The sole rejection in this case is that Claims 6-7 and 9-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Raymond, U.S. Patent No. 5,693,462, in view of Massoudy *et al.* (J. Mol. Cell. Cardiol. 29, 535-544). The Examiner's position is:

> Massoudy et al. teaches that cyclosporine A acts as a cardioprotective agent in ischemia and reperfusion (Abstract). Cyclosporine A, in concentrations of 0.8 μm in Krebs-Henseleit buffer, was shown to significantly prevent the loss of post-ischemic cardiac function in isolated hearts (p.536, col. 2, last ¶; p. 539, col. 2, 1st ¶). The reference does not teach the preferred concentration.

> Raymond teaches the components of the Krebs-Henseleit buffer as comprising those components as instantly claimed (col. 4, lines 15-33).
>
> It would have been obvious, absent a showing of unexpected results, to one of ordinary skill in the art at the time of the invention to treat an isolated heart with a composition comprising the claimed amount of cyclosporine A because Massoudy et al. teach that such compositions are useful at preserving the heart and "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).
>
> *Final Rejection dated September 9, 2005 at pages 2-3.*

The Examiner then alleges that the methods of Massoudy et al. and those as instantly claimed are both directed to preserving of a heart. *Final Rejection dated September 9, 2005 at page 3.*

7. ***Argument.***

Method Claim 6 limits the claim to "consisting essentially of". Claims 7 and 9-10 depend from Claim 6. Claims 11-14 are directed to a medicament and are cast in "consisting essentially of" terms. It is well-settled that the transitional phrase "consisting essentially of" only opens the claims to the inclusion of ingredients that would not materially affect the *basic* and *novel* characteristic of the claim. *In re Herz*, 453 F.2d 549, 190 USPQ 461, 463 (CCPA 1976); M.P.E.P. §2111.03 [R-2].

The Raymond Patent

The Raymond preservation solution does not teach or suggest the utilization of cyclosporin A in the methods or medicaments disclosed therein. What the Raymond patent does teach is a preservation solution for preserving and storing organs comprising:

(a) an isotonic solution;

(b) an amiloride-containing compound;

(c) adenosine; and

(d) water.

The active ingredients in the Raymond solution that materially affect the preserving properties are the amiloride-containing compound and adenosine. On the other hand, the active and material ingredient in the preservation solution of the claimed methods and medicament is cyclosporin A. Raymond does not teach the utilization of cyclosporin A in the methods or medicament disclosed therein. The method of Raymond includes a medicament that requires the use of an amiloride-containing compound and adenosine. These active products are excluded in the claims of the subject invention by the use of the limiting transitional phrase -- consisting essentially of --.

The Massoudy et al. Article

Massoudy et al. is not directed to preserving a heart *awaiting* transplantation. Massoudy *et al.* teach that cyclosporin A acts as a cardioprotective agent in ischemia and reperfusion *after* transplantation. According to the Examiner, cyclosporin A, at a concentration of 0.8 μM in Krebs-Henseleit buffer, was shown to significantly prevent the loss of post-ischemic cardiac function. The Examiner argues that

> One would have been *motivated* to add cyclosporin A of Massoudy *et al.* to the composition of Raymond because of an *expectation of success* in improving the cardio protective characteristics thereof. *Office Action dated June 20, 2005 at page 3.*

The Examiner points to page 537 of Massoudy *et al.* to show that cyclosporin A is used to concentrations of *0.08 μM and 0.8 μM* as the effective plasma level required in patients after heart transplantation. However, independent Claims 6 and 11 require that the amount of cyclosporin A is present in an amount of about *2.5 μM to about 10 μM* per liter of solution. The lower level cyclosporin A claimed is **at least three times** the amount of cyclosporin A disclosed in Massoudy *et al.* The reason for that in the claimed invention the heart is being preserved awaiting transplantation; not treated after implantation. Thus, the effects of cyclosporin A would be expected to be very different.

There is No Suggestion Or Motivation To Combine

Massoudy et al. With Raymond

Even if Raymond and Massoudy *et al.* were to be combined, they would not teach the claimed invention because the medicament and method of Raymond would necessarily include the use of an amiloride-containing compound and adenosine. Also, the amount of cyclosporin A taught in Massoudy *et al.* is at least 1/3 lower than that claimed.

A 15 minute interruption of blood flow and reperfusion which Massoudy *et al.* describe in their article, has little or no relationship to the claimed method for blocking apoptosis during preserving and storing a heart. The major alteration in the canine preserved heart at 18 hours is the appearance of apoptotic cells that indicate a programmed cell death and also the reason that permanent damage occurs in the myocardium. This kind of damage is not seen in the Massoudy *et al.* process. Actually, the Applicant did not find apoptotic cells in the solutions used in the claimed method until after 12 hours of preservation. Irreversible damage occurs when apoptotic cells are detected at 18 hours. *The unique finding is that cyclosporin A prevents apoptosis and therefore prolongs the preservation time for the heart.*

Preventing apoptosis has nothing to do with the findings that Massoudy *et al.* mention at this stage with a nitric oxide-dependent mechanism impeded by endothelin. Massoudy *et al.* disclose a reperfusion solution in which cyclosporin A is present in an amount of only 0.8 μM per liter. The Massoudy *et al.* article does not teach use of Raymond's amiloride in any type of solution whatsoever in the claimed amount. Massoudy *et al.* deal with a completely different technical problem over the present application, which is to minimize the reperfusion entry following the ischemic event. The teachings of Massoudy *et al.* show that the level of venous NO recovers faster after the ischemic episode and remains stable if the heart is perfused with the isotonic solution comprising cyclosporin A. Massoudy *et al.* is silent about the effects on an isolated heart preserved in the isotonic solutions disclosed in Massoudy *et al.* Thus, departing from Raymond as the primary reference, there is no particular reason for which one skilled in the art would turn to Massoudy *et al.* because Massoudy does not suggest that the isotonic solution therein disclosed would be particularly suited for solutions for preserving and storing a heart awaiting transplantation.

Therefore, the proposed combination of the Raymond and Massoudy *et al.* references lacks the necessary motivation required to establish a *prima facie* case of obviousness.

Because of the fundamental differences between an amiloride-containing compound and adenosine on the one hand and cyclosporin A on the other, as outlined above, persons of skill in the art who are familiar with both would not consider the substituting one for the other. The preservation solution of Raymond does not contemplate blocking apoptosis during preserving and storing a heart. Furthermore, the fact that a cyclosporin A-containing agent may have been successfully used in reperfusion treatment after implantation, as taught by Massoudy *et al.*, says nothing about whether this could be successfully implemented to block apoptosis using an entirely different solution after 18 hours or 24 hours. The Examiner's justification for this combination of solutions that both Raymond and Massoudy *et al.* improve "the cardio protective characteristics" is inadequate and not grounded in fact or in law. For these reasons, the rejection also lacks the second requisite of establishing a *prima facie* case of obviousness.

It is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness. It is submitted that the Examiner must, *inter alia*, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Thrift*, 63 USPQ.2d 2002, 2006 (Fed. Cir. 2002). The factual inquiry of whether to combine references must be thorough in searching and cannot be performed willy-nilly through the use of hindsight. Thus, the reason for there being some teaching, motivation or suggestion to select and combine portions of the references relied upon as evidence of obviousness in such manner as the claims. Furthermore, deficiencies in the cited references cannot be remedied by general conclusions about what is "basic knowledge". *In re Sang Su Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002).

Assuming that some reasonable motivation existed for modifying the Raymond method and solution in light of the Massoudy *et al.* teachings, this modification should lead to placing Massoudy *et al.*'s cyclosporin A into the solution of Raymond containing an amiloride-containing compound and adenosine. However, in order to arrive at Applicant's claimed invention, it is necessary to take Massoudy *et al.*'s specific teaching with respect to cyclosporin

A and to apply it to an entirely different solution at an entirely different level of cyclosporin A than taught.

From the foregoing, it should be evident that a hindsight reliance upon Applicant's own disclosure is the only conceivable basis why one would combine the Raymond and Massoudy *et al.* references in the manner set forth in the rejection. This is not a proper basis for an obviousness rejection.

8. ***Claims Appendix.***

An appendix containing a copy of the claims involved in the appeal is attached.

9. ***Evidence Appendix.***

There is no evidence appendix.

10. ***Related Proceedings Appendix.***

There are no related proceedings.

CONCLUSION

It is respectfully submitted that the claims, as presently amended, are not obvious over Raymond in view of Massoudy *et al.* Specifically, neither of the references teach adding cyclosporin A to any kind of solution whatsoever in the amounts claimed. In fact, Raymond does not use cyclosporin A at all; Raymond uses other active components. Massoudy *et al.* describes a process for a different purpose and does not use cyclosporin A in the amounts

claimed. It is, therefore, respectfully submitted that the cited prior art does not create a *prima facie* case of obviousness and the methods claimed in Claims 6-7 and 9-10 and the medicament of Claims 11-14 are not obvious.

Respectfully submitted,

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Janet F. Sherrill

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CLAIMS APPENDIX

1-5. (Cancelled)

6. (Previously Presented) A method for blocking apoptosis during preserving and storing a heart awaiting transplantation comprising:

perfusing said heart for up to 24 hours with a solution consisting essentially of:

(a) a balanced isotonic solution in a physiologically acceptable amount;

(b) cyclosporin A in an amount from about 2.5 μM to about 10 μM per liter of solution; and

(c) water.

7. (Original) The method according to Claim 6 wherein said balanced isotonic solution includes sodium, potassium, calcium, magnesium ions and bicarbonate.

8. (Cancelled)

9. (Previously Presented) The method according to Claim 6 wherein said cyclosporin A is present in an amount from about 5.0 μM to about 8.0 μM per liter of solution.

10. (Previously Presented) The method according to Claim 6 wherein said balanced isotonic solution comprises:

Concentration Ranges in 1 Liter	
NaCl	85 mM to 145 mM
KCl	3 mM to 50 mM
$CaCl_2$	0.5 mM to 2.5 mM
KH_2PO_4	0.7 mM to 1.3 mM
$MgSO_4$	0.9 mM to 4.8 mM
$NaHCO_3$	15 mM to 35 mM
Glucose	1.0 mM to 50 mM

11. (Previously Presented) A medicament for preserving and storing a heart while awaiting transplantation consisting essentially of:

(a) a balanced isotonic solution in a physiologically acceptable amount;

(b) cyclosporin A in an amount from about 2.5 μM to about 10 μM per liter of solution; and

(c) the remaining being water,

whereby said heart awaiting transplantation is preserved for up to 24 hours.

12. (Previously Presented) The medicament according to Claim 11 wherein said balanced isotonic solution includes sodium, potassium, calcium, magnesium ions and bicarbonate.

13. (Previously Presented) The medicament according to Claim 11 wherein said cyclosporin A is present in an amount from about 5.0 μM to about 8.0 μM per liter of solution.

14. (Previously Presented) The medicament according to Claim 11 wherein said balanced isotonic solution comprises:

Concentration Ranges in 1 Liter	
NaCl	85 mM to 145 mM
KCl	3 mM to 50 mM
$CaCl_2$	0.5 mM to 2.5 mM
KH_2PO_4	0.7 mM to 1.3 mM
$MgSO_4$	0.9 mM to 4.8 mM
$NaHCO_3$	15 mM to 35 mM
Glucose	1.0 mM to 50 mM